PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003029	22.03.2004	24.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/12, A61K39/29, A61K39/39, A61K38/00, A61P31/00

Applicant
INTERCELL AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/003029

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14 (IA)

because:

☒ the said international application, or the said claims Nos. 14 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,6,11,12
	No:	Claims	1-4,7-10,13-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-13,15
	No:	Claims	

2. Citations and explanations

see separate sheet

Item III

III.1 With respect to claim 14

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Item V

V.1 Reference is made to following documents

D1: L. VERNACCHIO ET AL.: 'Effect of monophosphoryl lipid A (MPL®) on T-helper cells when administered as an adjuvant with pneumococcal-CRM197 caonjugate vaccine in healthy toddlers', VACCINE, 2002, vol. 20, pages 3658-3667

D2: WO0154719 (SMITHKLINE BEECHAM BIOLOGICALS S.A.) 02 August 2001 (2001-08-02)

D3: WO0023105 (SMITHKLINE BEECHAM BIOLOGICALS S.A.) 27 April 2000 (2000-04-27)

D4: WO0117551 (SMITHKLINE BEECHAM BIOLOGICALS S.A.) 15 March 2001 (2001-03-15)

D5: WO9815287 (SMITHKLINE BEECHAM BIOLOGICALS S.A.) 16 April 1998 (1998-04-16)

D6: WO9933488 (SMITHKLINE BEECHAM BIOLOGICALS S.A.) 08 July 1999 (1999-07-08)

D7: M. J. McCLUSKIE ET AL.: 'Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and CpG DNA', FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, 2002, vol. 32, pages 179-185

D8: WO0193905 (CISTEM BIOTECHNOLOGIES GMBH) 13 December 2001 (2001-12-13)

D9: WO02053185 (INTERCELL BIOMEDIZINISCHE FORSCHUNGS- UND ENTWICKLUNGS AG & CISTEM BIOTECHNOLOGIES GMBH) 11 July 2002 (2002-07-11)

D10: WO0232451 (CISTEM BIOTECHNOLOGIES GMBH) 25 April 2002 (2002-04-25)

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 1-4, 7-10, and 13-15

The **document D1** describes vaccine compositions comprising a pneumococcal-CRM197 conjugate antigen, alum and MPL (abstract). **Document D2** describes vaccine compositions comprising HIV antigens, alum and saponins, such as QS21 and/or MPL inducing a TH1 immun response (p. 6 2nd-4th paragraph, p. 8 3rd-4th paragraph, p. 10 1st paragraph, p. 13 2nd paragraph). **Document D3** describes vaccine compositions comprising an antigen, such as antigens derived from HAV, HBV (i.e. HBsAg), HCV, hepatitis D virus, hepatitis E virus (p. 7 l. 11 - p. 8 l. 31), alum (AL(OH)3 or ALPO4) and either monophosphoryl lipid A, saponins, such as QS21 or Quil A (p. 6 l. 18-27), ISS-ODN such as CPG, or block copolymers (p. 4 l. 24 - p. 5 l. 31). **Document D4** describes vaccine compositions comprising viral antigens derived from HPV, HAV, HSV, HBV (HbsAg) or antigens derived from the parasite Toxoplasma gondii, alum and 3D-MPL (p. 5 l. 21-23, p. 7 l. 16 - p. 8 l. 30, p. 10 l. 20, p. 11 l. 26 - p. 12 l. 20, p. 15 l. 1-8, p. 16 l. 22-25). Said vaccine compositions induce a TH1 immune response (p. 5 l. 29 - p. 7 l. 14). **Document D5** describes vaccine compositions comprising an antigen such as HBsAg, alum, MPL, QS21, and small unilamellar vesicles inducing TH1 immune responses against viral, bacterial, parasitic infections (p. 1 l. 19-23, p. 3 l. 12 - p. 5 l. 24, p. 6 l. 26-29, Examples 1-3, and 5). Therefore, vaccine compositions comprising an antigen, a Th1 immune response inducing adjuvant and alum are generally known in the field. Therefore, the subject-matter of claims 1-4, 7-10 and 13-15 is not considered novel in the sense of Article 33(2) EPC.

V.2.2 With respect to claims 7-10, 13 and 14

The subject-matter of claims 7-10, 13, and 14 does not disclaim the use of vaccine compositions comprising an antigen, alum and ISS-ODN being an CpG ODN. Therefore, **documents D6** and **D7** disclosing vaccine compositions comprising an antigen such as HbsAg, alum and CpG ODN (D6: p. 8 Example 1; D7: abstract, Table 1, p. 184 left-hand col. 2nd paragraph) are considered to be novelty destroying for said claims. Therefore, claims 7-10, 13, and 14 are not considered novel in the sense of Article 33(2) PCT.

V.2.3 With respect to claims 5, 6, 11, and 12

None of the documents cited in the international search report disclose a vaccine composition comprising an antigen, Alum and either an ISS-ODN selected from the

group disclosed in claims 5 and 11 or a polycationic polymer selected from the group disclosed in claims 6 and 12. Therefore, the subject-matter of claims 5, 6, 11, and 12 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 5, 6, 11, and 12

The subject-matter of claims 5, 6, 11, and 12 differs from the closest prior art **documents D1-D5** in that the TH1 immune response inducing adjuvant is a ISS-ODN as defined in claims 5 and 11 or a polycationic polymer as defined in claims 6 and 12. The technical problem to be solved resides in the provision of an alternative vaccine composition comprising an antigen, alum and a TH1 immune response inducing adjuvant. **Document D8** describes the type 1 adjuvant activity of ISS-ODN comprising e.g. deoxyinosine, deoxyuridine (abstract, p. 4 2nd paragraph - p. 6 2nd paragraph). Furthermore, **D8-D10** disclose polycationic polymers such as polyarginine, polylysine and cathelicidin having adjuvant activity (D8: p. 12 1st paragraph - p. 13 4th paragraph; D9: p. 3 2nd paragraph - p. 5 1st paragraph; D10: p. 3 2nd paragraph, p. 5 2nd paragraph - p. 7 1st paragraph, p. 12 4th paragraph - p. 13 4th paragraph). Therefore, the subject-matter of claims 5, 6, 11, and 12 is not considered inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-13 and 15

The subject-matter of claims 1-13 and 15 appears to be susceptible of industrial application.

V.4.2 With respect to claim 14

The subject-matter of claim 14 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claim 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound

for the manufacture of a medicament for a new medical treatment.

V.5 Further remarks

V.5.1 With respect to claims 1-15

The expression "a type 1 inducing adjuvant" does not appear to be clear, since the generally used expression would be "a TH1 immune response inducing adjuvant" (Article 6 PCT).

V.5.2 With respect to claim 13

Claim 13 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, i.e the enhancement of a TH1 immune response, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.